

- a) inputting a protein backbone scaffold;
  - b) applying a first protein design cycle comprising at least one heuristic component to said scaffold to generate at least a first variable sequence;
  - c) applying a second protein design cycle comprising at least one heuristic component to said scaffold to generate at least a second variable sequence; and
  - d) generating a probability matrix comprising at least said first and second variable sequences.
19. (New) A method according to claim 18 wherein said first and second protein design cycle comprise the same components.
20. (New) A method according to claim 18 wherein said first and second protein design cycle comprise different components.
21. (New) A method according to claim 18 wherein at least one of said heuristic components comprises a genetic algorithm.
22. (New) A method according to claim 18 wherein at least one of said heuristic components comprises a Monte Carlo algorithm.
23. (New) A method according to claim 21 wherein at least one of said first and second protein design cycles comprises a self consistent mean field theory (SCMF) algorithm.
24. (New) A method according to claim 22 wherein at least one

of said first and second protein design cycles comprises a self consistent mean field theory (SCMF) algorithm.

25. (New) A method according to claim 21 wherein at least one of said first and second protein design cycles comprises a dead end elimination (DEE) algorithm.

26. (New) A method according to claim 22 wherein at least one of said first and second protein design cycles comprises a dead end elimination (DEE) algorithm.

27. (New) A method according to claim 18 wherein said probability matrix comprises a summation of the variable sequences generated for each scaffold.

28. (New) A method according to claim 18 wherein said probability matrix comprises a recombination of some or all of the variable sequences generated for each scaffold.

29. (New) A method according to claim 18 further comprising ranking said variable sequences.

30. (New) A method according to claim 18 further comprising synthesizing a plurality of said sequences

31. (New) A method according to claim 18 further comprising recombining a plurality of said variable sequences to form additional variable sequences.

32. (New) A method executed by a computer under the control of a

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program, said computer including a memory for storing said program, said method comprising the steps of:

- a) inputting an ensemble of protein backbone scaffolds;
- b) applying a protein design cycle to each of said scaffolds to generate at least one variable sequence; and
- c) generating a probability matrix comprising a plurality of the variable sequences generated in step b).

33. (New) A method according to claim 32 wherein said probability matrix comprises a summation of the variable sequences generated for each scaffold.

34. (New) A method according to claim 32 wherein said probability matrix comprises a recombination of some or all of the variable sequences generated for each scaffold.

35. (New) A method according to claim 32 wherein said protein design cycle comprises a genetic algorithm.

36. (New) A method according to claim 32 wherein said protein design cycle comprises a Monte Carlo algorithm.

37. (New) A method according to claim 32 wherein said protein design cycle comprises a self consistent mean field theory (SCMF) algorithm.

38. (New) A method according to claim 32 wherein said protein design cycle comprises a dead end elimination (DEE) algorithm.

39. (New) A method according to claim 32 wherein said ensemble comprises a family of naturally occurring proteins.

40. (New) A method according to claim 32 wherein said ensemble is generated by a Monte Carlo simulation.

41. (New) A method according to claim 32 further comprising ranking said variable sequences.

42. (New) A method according to claim 32 further comprising synthesizing a plurality of said sequences.

43. (New) A method according to claim 32 further comprising recombining a plurality of said variable sequences to form additional variable sequences.

44. (New) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

- a) inputting at least one protein backbone scaffold;
- b) applying a protein design cycle to generate at least a first variable nucleated state sequence;
- c) sequentially altering in said nucleated state sequence a plurality of amino acids by testing a plurality of rotamers for each amino acid change and calculating the energy of each altered sequence; and

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